1,095,552

PATENT SPECIFICATION 1,095,552

DRAWINGS ATTACHED.

Date of Application and filing Complete Specification:
Feb. 16, 1965. *No. 6625/65.*

Application made in United States of America (No. 346,438) on Feb. 21, 1964.

Complete Specification Published: Dec. 20, 1967.

Index at Acceptance:—D1 R3; B5 B(2C4, 3B).

Int. Cl.:—D 04 h 1/00.

COMPLETE SPECIFICATION.

Improvements relating to Collagen Films and Process for making them.

We, ETHICON, INC., a Corporation of the State of New Jersey, United States of America located at Somerville, New Jersey, United States of America, do hereby declare the invention, for which we pray that a

ERRATUM

SPECIFICATION NO. 1,095,552

Page 1, Title *for* "PROCESS" *read* "PROCESSES"

THE PATENT OFFICE,
5th June 1968

D 104295/8

tion to a diameter of about 2,000 to about 90,000 Angstrom units.

The term "filament", as used herein, means a single thread of oriented collagen fibrils as extruded through a single orifice in a spinnerette.

The term "multifilament," as used herein, means a group of individual separate collagen filaments extruded through a spinnerette.

The term "tape," as used herein, means a group of individual filaments that have been united to form a unitary structure that is ribbon-like in shape.

The term "strand," as used herein, means a group of individual filaments that have been united to form a unitary structure of circular cross-section.

The term "film" as used herein, means a sheet having substantially greater area than thickness.

The repair of soft body tissues, such as the liver and spleen, has always been a difficult problem for the surgeon because attempts to suture such tissues frequently result in the suture tearing out. The cross-sectional area of the suture is so small that the force applied by the surgeon to position and tie the suture may cut through the soft tissue being repaired. Even in those instances where the surgeon may succeed in sources leaves much to be desired.

Attempts have been made to provide a substitute for fascia lata by preparing a dispersion of collagen and casting a film. It is a disadvantage of collagen films prepared by this procedure that they do not have the desired tear strength.

It is an object of the present invention therefore to provide a collagen film having high tear-strength that is useful in surgery.

While the present invention is not to be limited to any particular theory of operation the stitch tear strength of collagen films is believed to be a function of the arrangement of the collagen fibrils in the films. It has been demonstrated that when films are made by casting a dispersion of swollen collagen fibrils, the fibrils become arranged in broad sheets in which they lie parallel to the surfaces of the film but are randomly oriented with respect to each other. Fibers, consisting of naturally-formed bundles of fibrils oriented parallel to each other, are lacking entirely.

According to the invention, there is provided a collagenous film comprising a mul-

[*Price 4s. 6d.*]

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Improvements relating to Collagen Films and Process for making them.

We, ETHICON, INC., a Corporation of the State of New Jersey, United States of America located at Somerville, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a collagen film that is useful in surgery, and to a method of manufacturing such a film.

For the sake of clarity, the terms used herein are defined as follows:—

The term "swollen collagen fibril", as used herein, means a thread-like collagen structure that has been swollen in acid solution to a diameter of about 2,000 to about 90,000 Angstrom units.

The term "filament", as used herein, means a single thread of oriented collagen fibrils as extruded through a single orifice in a spinnerette.

The term "multifilament," as used herein, means a group of individual separate collagen filaments extruded through a spinnerette.

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The term "film" as used herein, means a sheet having substantially greater area than thickness.

The repair of soft body tissues, such as the liver and spleen, has always been a difficult problem for the surgeon because attempts to suture such tissues frequently result in the suture tearing out. The cross-sectional area of the suture is so small that the force applied by the surgeon to position and tie the suture may cut through the soft tissue being repaired. Even in those instances where the surgeon may succeed in placing the sutures without undue damage to the soft tissue, the sutures may tear out before healing is complete. It has become the practice, therefore, in operations of this type, and also in the repair of body defects where maximum strength is required, to suture through a sheet of absorbable material such as fascia lata which holds the suture until healing has taken place. Unfortunately thin sheets of fascia lata also have poor tear strength and the uniformity of this material which is derived from animal sources leaves much to be desired.

Attempts have been made to provide a substitute for fascia lata by preparing a dispersion of collagen and casting a film. It is a disadvantage of collagen films prepared by this procedure that they do not have the desired tear strength.

It is an object of the present invention therefore to provide a collagen film having high tear-strength that is useful in surgery.

While the present invention is not to be limited to any particular theory of operation the stitch tear strength of collagen films is believed to be a function of the arrangement of the collagen fibrils in the films. It has been demonstrated that when films are made by casting a dispersion of swollen collagen fibrils, the fibrils become arranged in broad sheets in which they lie parallel to the surfaces of the film but are randomly oriented with respect to each other. Fibers, consisting of naturally-formed bundles of fibrils oriented parallel to each other, are lacking entirely.

According to the invention, there is provided a collagenous film comprising a mul-

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tiplicity of filaments consisting essentially of collagen fibrils, the said filaments being randomly arranged in the plane defined by the film and bonded to each other along their contiguous surfaces to form a unitary structure. Those films contain interlocking and anastomosing bundles of filaments in a pattern somewhat similar to that found in animal skins.

The collagenous film according to the invention may be made by extruding a homogeneous aqueous dispersion of pure swollen collagen fibrils into a dehydrating bath (e.g. a solution comprising acetone with 120—140 mg. of ammonia per litre of acetone and 40—60 grams of water per litre of acetone) to form a bundle of filaments. These bundles of filaments may be cut to various lengths and placed on a suitable support such as a screen to build up a layer of collagen filaments that are randomly oriented in planes parallel to the surface of the supporting screen. Alternatively, the bundle of collagen filaments may be further processed to obtain a strand or tape the individual filaments of which have longitudinal axes substantially parallel with the longitudinal axis of the strand or tape. Such strands or tapes are equally suitable for forming a layer of collagen supported by the screen. The layer of collagen filaments, strands, or tapes or a mixture thereof is then laminated and bonded together into a unitary structure by immersing the collagen layer and its supporting screen in a dilute aqueous acid solution.

Preferably, the dilute aqueous acid solution has dispersed therein swollen collagen fibrils. After the dilute aqueous acid solution has swollen the layer of collagen, the screen is raised out of the bath and air-dried in an atmosphere containing ammonia gas. The dried and neutralized film may then be washed with water to remove soluble ammonium salts, tanned to improve its wet strength, dried and then removed from its supporting screen. In the film produced the collagen tapes (or strands) retain their structural form, and the film consequently has a considerable tear strength.

The invention will appear more clearly from the following detailed description when taken in connection with the accompanying drawings, which show, by way of example, preferred embodiments of the inventive idea.

FIGURE 1 is a plan view, partly broken away, of a collagen film of the present invention.

FIGURE 2 is an enlarged edge view in cross-section of the film supported on a screen.

FIGURE 3 is an enlarged perspective view of a section of collagen tape.

FIGURE 4 is an enlarged sectional view of the collagen tape taken along the line 4—4 of FIGURE 3.

With reference to FIGURE 1 there is disclosed the structure of a collagen film 10 composed of a multiplicity of collagen tapes 11 randomly arranged in the plane defined by the surface 12 of the film. As best indicated in FIGURE 2, which greatly exaggerates for the purpose of clarity the separation between adjacent segments of tape, the tape segments are substantially parallel to the surfaces of the screen 13 and the film 12. In one embodiment of the present invention, a long segment of tape 14 may be randomly coiled and placed so that it is centrally located within the film between the top surface 12 and the bottom surface 15 thereof. The tape segments of which the film 10 is composed may conveniently be from about 1/8 inch to about 1/4 inch in width and are visible to the naked eye. The orientation of the tape segments within the film will, however, be more vividly apparent if the film is examined under a polarized light due to the intrinsic birefringence of the filaments resulting from the rectilinear arrangement of the fibrils parallel to the longitudinal axis of the filaments. The parallel arrangement of the collagen filaments 16 in the tape 11 will be readily understood from FIGURES 3 and 4. The collagen fibrils that make up the filaments 16 have the typical banding at intervals of approximately 640 Angstrom units that is characteristic of collagen fibrils in their natural state.

The manufacture of a collagen film having outstanding tear strength will be illustrated by the following examples. Throughout the specification all quantities are expressed in parts by weight unless otherwise indicated.

EXAMPLE I

500 parts of the dispersion of swollen collagen fibrils described in Example II of Patent Specification No. 915,066 (viz. a dispersion obtained from sliced bovine deep flexor tendon by treatment with a solution containing the enzyme ficin followed by treatment with aqueous-methanolic cyanoacetic acid) is diluted with 3500 parts of water. The collagen dispersion prior to dilution contained 0.86% collagen solids and 0.38% cyanoacetic acid in equal parts by volume water and methanol.

It has been empirically determined that when using a screen having an area of about 180 square inches, approximately one gram of collagen tape is required for each mil thickness of the finished stitchable film. Ten grams of untanned collagen tape prepared as described in Patent Specification No. 1,019,712 (that is to say, by extruding a dispersion of swollen collagen fibrils into a dehydrating bath to form a ribbon-like

extrusion made up of cohered individual filaments, which is then suitably processed) is cut into random lengths ranging from about 1 centimeter to 10 centimeters and laid on a stainless steel screen measuring 10 inches by 18 inches. The pore size of the screen is not critical and may vary from about 100 square mils to about 10,000 square mils. The cuttings are dropped onto the filming screen so that they are uniformly distributed and randomly oriented. A long length of collagen tape (about 3 meters) is randomly coiled over the cuttings. Another 10 grams of collagen tape is cut into random length and distributed over the coiled tape and the screen surface as before. The long length of tape in between two layers of short lengths serves to minimize drifting of the tape segments in the next step of the process.

The screen with the tape cuttings on it is placed in a large tray. A sufficient quantity of ethanol (95%) is poured into the tray *outside* of the screen so that it wells up through the screen and wets the tape. This will reduce bubble formation from entrapped air when the dilute collagen dispersion is introduced. It is essential to avoid an excess of ethanol in this step. Next, the dilute collagen dispersion described above is poured into the tray *outside* of the screen so that it wells up through the screen without disturbing the distribution or orientation of the collagen tape cuttings. The depth of the dilute dispersion over the screen should be about 100 times the desired thickness of the finished film. Within a few minutes, the collagen tape begins to swell and becomes translucent. When the tape is sufficiently swollen (about 2 hours) the filming screen with the swollen tapes supported thereon is removed from the tray and placed over a second tray containing 20 parts of concentrated aqueous ammonium hydroxide. This causes the collagen fibrils to shrink from the bottom up, i.e., the collagen fibrils that are in contact with the stainless steel screen shrink first. The large amount of free fluid liberated as the collagen fibrils shrink drains through the screen and serves to compact the shrunken fibrils against the screen. For films 10—15 mils thick this process may be completed overnight.

The screen is uncovered and removed from the shrinking tray. Excess moisture is removed by placing the bottom of the screen on sufficient thicknesses of cotton towel. When it is seen that excess fluid has been removed, the screen may be propped up so that the film can dry from both surfaces. Drying can be accelerated by the use of a fan (without heat).

After drying, the film measures about 15 mils in thickness. It may be tanned while still attached to the screen to preserve its flatness. The film is washed on the screen and then immersed for 2 hours in a solution containing 3 parts of formalin (36% CH_2O) in 100 parts of water. The film and its supporting screen is removed from the tanning bath and air-dried. The film should not be removed from the screen until it is completely dry after tanning.

EXAMPLE II

Untanned collagen tape is swollen in a dilute aqueous acid dispersion of collagen fibrils as described in Example I above. After 15 minutes the supporting screen is placed over a pan containing about 10 parts of ammonium hydroxide to simultaneously shrink the collagen fibrils and remove excess fluid. After 2 days a thick mat of shrunken collagen fibrils remains on the screen. This is allowed to dry for 2 more days and then excess fluid is blotted out by placing the mat between layers of cotton towels for an additional day. The mat is finally dried to the translucent (glass) state by tacking it to a curtain stretcher. The dried sheet is approximately 125 mils thick. When examined in polarized light both microscopically and macroscopically, it is seen that the sheet is composed mainly of randomly arranged collagen tapes. A small portion of the sheet is tanned with formaldehyde. It has good stitch tear properties.

EXAMPLE III

Twenty parts of collagen strands are swollen in 4,000 parts of the collagen dispersion described in Example I above. Swelling is done without agitation so that the collagen fibrils remain organized in parallel bundles. The swollen strand is spread on a filming screen and suspended over a tray containing about 10 parts of ammonium hydroxide. The fibrils shrink and most of the free fluid drains off overnight. After washing the wet mat with water, it is permitted to dry into a translucent film ranging from five to ten mils in thickness. A portion of the film is tanned with formaldehyde as described in Example I above. When wet, it has good stitch tear properties. Examination in polarized light reveals that the collagen is organized as randomly arranged strands.

EXAMPLE IV

The procedure of Example III is followed with 10 parts of collagen tape and 4 000 parts of the dilute dispersion of swollen collagen fibrils described in Example I. The tape is cut into lengths averaging about 2 inches. The film is lightly tanned with a 1% solution of formalin in water for about one hour. The dry film obtained is brittle but, when soaked in water for about 15 minutes, the stitch tear strength is obvi-

ously superior to that of films made by casting a dispersion of swollen fibrils.

Stitch tear determinations are made on the Scott tester. The film is cut into strips measuring 1/2 inch by 2—1/2 inches. One end of each strip is fastened in one of the clamps of the Scott tester. The other end is fastened to a hook made of wire about 25 mils in diameter which is held securely in the other clamp of the tester. The film strips are perforated on their center lines 1/4 inch in from the edge. The films are soaked in water for 15 minutes before testing. A film made by the casting process is used as a comparative control. The results are tabulated in the following table:—

	Control	*Experimental*
Dry Thickness	15 mils	8 mils
Wet Thickness	34 mils	9 mils
Tear Strength	2.3 lbs.	3.6 lbs.

In all instances, the hook tears directly out of the control film parallel to the stress direction. In the experimental films, the tear in the film is at right angles to the stress direction.

On a per mil dry thickness basis, the control films average 0.153 lbs. tear strength while the experimental films averaged 0.450 lbs., a threefold difference

WHAT WE CLAIM IS:—

1. A collagenous film comprising a multiplicity of filaments consisting essentially of collagen fibrils, the said filaments being randomly arranged in the plane defined by the film and bonded to each other along their contiguous surfaces to form a unitary structure.

2. The collagenous film of Claim 1, wherein substantially all of said fibrils are aligned parallel to the longitudinal axis of the respective filaments of which they form a part and wherein the fibrils throughout their entire length are arranged in said filaments, as in their natural state, in a manner showing typical banding at intervals of approximately 640 Angstrom units and substantial rectilinearity.

3. The collagenous film of Claim 1 or Claim 2, wherein the filaments are grouped in tapes, the tapes being disposed and bonded to each other as defined in Claim 1 regarding the filaments.

4. The collagenous film according to Claims 1 or 2, wherein the filaments are grouped in strands which are disposed and bonded together in the manner defined in Claim 1 regarding the filaments.

5. The collagenous film according to any one of Claims 1 to 4, wherein the film has opposed principal faces with substantially the same spacing throughout their extent.

6. The collagenous film of any one of Claims 1 to 5, wherein the film is free of elastin.

7. The collagenous film of any one of Claims 1 to 6, wherein the film is impregnated with a collagen tanning agent.

8. The process of making a collagenous film as claimed in any one of Claims 1 to 7, wherein individual lengths of filaments or tapes or strands are deposited in a random manner on a foraminous supporting surface to form a layer of uniform thickness, the layer is immersed (while still on the supporting surface) in a dispersion of swollen collagen fibrils in an acid aqueous liquid, the filaments or tapes or strands are permitted to swell in the dispersion, the surplus dispersion is allowed to drain from the layer while still on the supporting surface, and the layer is permitted to dry in air containing ammonia gas, whereby the swollen filaments or tapes or strands are caused to shrink and become bonded together to form a film which is subsequently removed from the foraminous supporting surface.

9. A process according to Claim 8, in which the film formed is washed with water to remove soluble ammonium salts, tanned with an aqueous solution of a collagen tanning agent, dried and removed from the supporting surface.

10. The collagenous film substantially as described herein with reference to the accompanying drawings.

11. The process of making a collagenous film substantially as described herein with reference to the accompanying drawings.

12. A process of making a collagenous film, substantially as described in any of the Examples given above (not being a "control" process).

13. A collagenous film made by a process according to any of claims 8, 9, 11 and 12.

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1095552 COMPLETE SPECIFICATION

1 SHEET *This drawing is a reproduction of the Original on a reduced scale*

Fig.1.

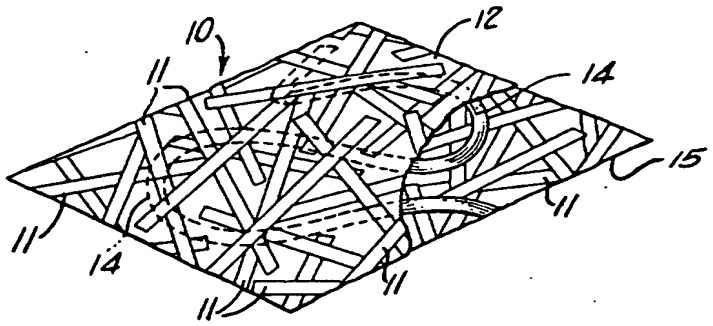

Fig.2.

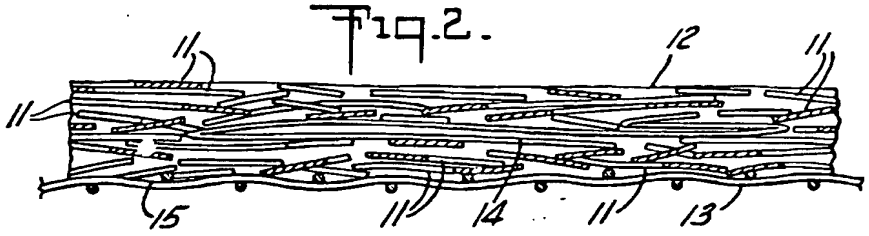

Fig.3.

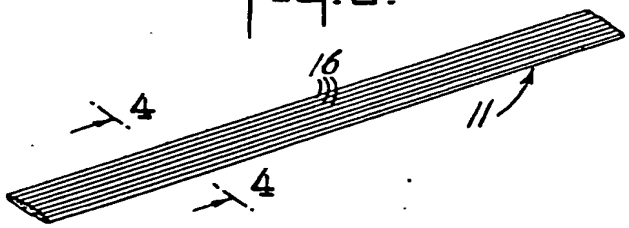

Fig.4.